IN THE UNITED STATES PATENT OFFICE

Application Serial No. 07/675,908

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Applicants: Dr. Rudolf Falk
Dr. Samuel S. Asculai
(Now assigned to
Hyal Pharmaceutical Corporation)

Title: THE USE OF HYALURONIC ACID OR ITS DERIVATIVES TO ENHANCE DELIVERY OF ANTINEOPLASTIC AGENTS

Inventors: Dr. Rudolf Falk,
Dr. Samuel S. Asculai

Examiner: Dr. Jacqueline Krikorian Ph.D. (*formerly* Dr. Stephen Martin, Ph.D.)

Group Art Unit: 1806 Extended Due Date: September 5, 1996

The Commissioner of Patents
UNITED STATES PATENT OFFICE
2011 Jefferson Davis Highway
Crystal Plaza 2, Room 1B03
Arlington, Virginia
U.S.A. 22202

DECLARATION OF GEORGE A. DEVEBER
under § 1.132

I, GEORGE A. DEVEBER, make oath and say as follows:

1. I am a Medical Doctor qualified in general internal medicine (FRCP) (C) and a practicing nephrologist for in excess of 30 years now, certified by the American Board of Internal Medicine. I obtained my medical undergraduate degree from the University of Toronto.

2. Now shown to me and marked as ***Exhibits*** *"1"* and *"2"* to this my Declaration is a copy of my Curriculum Vitae and Bibliography respectively.

3. I am a Medical Consultant to the Assignee, Hyal Pharmaceutical Corporation, of U.S. Patent Application Serial No. 07/675,908 which is, I am advised by Ivor Hughes, Counsel to Hyal Pharmaceutical Corporation, the National Entry Application into the United States from PCT International Publication No. WO 91/04058 filed September 18, 1990.

4. As a Medical Consultant, I was involved in advising Hyal Pharmaceutical Corporation and have carried out research and development and testing for Hyal Pharmaceutical Corporation. I would not, however, let my acting as a Consultant for Hyal Pharmaceutical Corporation or for anyone, interfere with or cloud my professional objectivity and responsibilities in preparing any declaration.

5. I consider myself to have in-depth knowledge of the products of Hyal and their use and application. These products include forms of hyaluronic acid for example, sodium hyaluronate having various molecular weights, amounts and percentage concentrations. I have, as well, written confidential articles with respect to the medical applications and uses of hyaluronic acid. These articles are kept on file at Hyal Pharmaceutical Corporation's offices.

6. I was asked by Counsel to Hyal to review the contents of International Publication No. WO 91/04058 and asked to determine if persons skilled in the art reading the document are taught how to formulate the dosages to be administered and how to administer the dosages.

7. I have carefully reviewed International Publication No. WO 91/04058 and, in my opinion, the relative skill of those in the field of medicine is commonly recognized as being high, that is, a person with a Ph.D., medical or similar degree, and several years of bench or clinical experience.

8. As a result, I have concluded that in respect of the preparation and use of the dosages taught in the said Application, persons skilled in the art would have sufficient information from the Application to prepare and use the dosages for the treatment of disease and conditions for which a medicine or therapeutic agent may be used.

9. In my opinion, the invention of the International Publication No. WO 91/04058 is directed to the delivery (transport) of medicines and therapeutic agents which may be suitable for treating the diseases and conditions by altering the medicines and therapeutic agent's distribution and performance in the human body producing an unusual targeting for pathological tissue (see p. 24, lines 13-17 of the International Publication No. WO 91/04058). If the disease or condition site in need of treatment would benefit from the use of a medicine or therapeutic agent administered then, the use of the hyaluronic acid and salts thereof would transport (deliver) the medicine/therapeutic agent to the site in need of treatment. This is accomplished according to the teachings of International Publication No. WO 91/04058 by administering hyaluronic acid or salts thereof.

10. When I speak of salts, I understand that term to mean "pharmaceutically acceptable salt" and these pharmaceutically acceptable salts must not be used in toxic amounts. Persons skilled in the art would understand this from the phrase "salts thereof". In my opinion, a practicing physician would be guilty of malpractice if the physician knowingly used toxic amounts or toxic salts without

extreme justification in the treatment of the patient. Thus, to me the expression "salts", "pharmaceutically acceptable salts", and "non-toxic salts" would be interchangeable with reference to this Application.

11. Additionally, International Publication No. WO 91/04058 specifies that to achieve this delivery (transport) of the medicines that between about 10 mg. to 1,000 mg. or more per 70 kg. person of the hyaluronic acid must be present in the dosage amount to provide the delivery/transport (see p. 26, line 33). The patent application specifies optimal doses of HA tending to range between 50 mg. and 350 mg. of HA per 70 kg. individual.

12. Exemplary amounts of hyaluronic acid are said to have molecular weights in the order of an average molecular weight of about 225,000 daltons (see p. 29, lines 35-36) where a 2% solution is provided, a mean average molecular weight within the range of 150,000 to 225,000 daltons (at p. 30, line 35), and a viscosity average molecular weight of less than 750,000 daltons (see p. 31, lines 33-34).

13.. Where high molecular weight hyaluronic acid is used in the dosages, it must be diluted to permit administration and ensure no intramuscular coagulation (p. 33).

14. In my opinion, persons skilled in the art preparing the dosages in this Application would not administer dosages that were not suitable. Such person would read the specification knowing that the hyaluronic acid and medicine would be put into dosage forms which could be administered easily for example, in intravenous administration. The practitioner would use HA and drugs in a dosage amount having the relevant viscosity having regard to the usual acceptable standards for administration such as intravenous administration. The same is true with the other routes of administration. Persons skilled in the art

would when combining the HA and medicine to form the dosages, be, in effect, diluting both the HA and medicine to form the dosages that were determined to be suitable.

15. International Publication No. WO 91/04058 is replete with various examples of the use of the dosage forms. Not only are the numbered Cases examples of the use but also, the anecdotal examples that have been provided in the body of the specification that are not identified as cases such as for example, beginning at page 24, line 14 to page 26, line 14, various examples of the use of the combinations; between page 51, line 26 to page 52, line 4, other examples are given and between page 33, line 37 and page 35, line 30 prefaced by the statement that "the Applicant has combined HA with medicinal and therapeutic agents for the treatment of conditions and diseases with totally unexpected results: for example". Eighteen (18) sub-paragraphs of examples follow.

16. In my opinion, the Application is thus replete with the examples of the unusual targeting (delivery) of medicines by the HA.

17. In the cases evidencing cancer treatment "in substantially all, if not all, cancer cases, the patient had been unresponsive to conventional treatment". This statement leads me to the conclusion that the responses of the patients (for example, better quality of life, extended survival) were as a result of the administration of the hyaluronic acid and medicine and the patients' responses were, in my opinion, unexpectedly high with regard to patients treated by conventional therapy. In fact, as stated at page 6, lines 4-6, "in substantially all, if not all cancer cases the patient had been unresponsive to convention treatment". In my opinion, this result was not as a result of spontaneous remission. In my experience, spontaneous remission of cancer in an advanced state where the

patient is unresponsive to conventional treatment, does occur, but is uncommon.

18. International Publication No. WO 91/04058 discusses use of HA to reduce the side effects of medicines such as NSAIDs for example, HA. This is discussed at page 25, lines 20, and lines 34-35:

> "When in excess of 200 mg. of the form of hyaluronic acid is used, no major toxic side effects occur such as gastro-intestinal distress, neurological abnormalities, depression, etc., even at elevated amounts of indomethacin (if necessary). "

This, of course, will vary from patient to patient. Some patients are more susceptible to side effects than other patients. This will have to be monitored by the physician.

19. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements will jeopardize the validity of the application and any patent issuing thereon.

EXECUTED this 28th day of August, 1996.

GEORGE A. DEVEBER

EXHIBIT 1

GEORGE A. DEVEBER, M.D., F.R.C.P.(C)

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CURRICULUM VITAE

SUMMARY

1. Experienced physician with extensive background in hospital, corporate and academic fields, including managerial and executive roles. Has developed key networking contacts throughout the healthcare, government, biotechnology and academic communities. Skilled in project management, staff recruitment and development. Current activities include Medical Director of Hyal Pharmaceutical Corporation, Vasogen Inc. and provision of consulting services to Baxter Corporation and Hyal Pharmaceutical Corporation.

EXPERIENCE - ACHIEVEMENTS

2. HYAL PHARMACEUTICAL CORPORATION — Jan. 1, 1994-present
Medical Director

(a) Responsibility in respect of clinical trials with respect to formulations using hyaluronic acid (sodium hyaluronate) alone or in conjunction with medicines for example the NSAID diclofenac;

(b) Wrote internal corporate review of Biology, Pharmacology clinical trials and potential applications of compositions containing hyaluronic acid (sodium hyaluronate).

3. VASOGEN INC. — 1994-present
Medical Director

(a) **Responsible** for clinical development, clinical trials and **regulatory affairs.**

4. BAXTER CORPORATION — 1987-1992
Vice-President Medical Affairs

(a) **Worked mainly with specialty product divisions, such as renal and cardiovascular, where end user influence is strong;**

(b) **Provided medical/scientific support regarding marketing, educational programs;**

(c) Provided medical liaison and support to Baxter's Canadian regulatory group with respect to new product submissions, clinical trials; dealt directly with Health Protection Branch (Canada);

(d) Assisted in designing and monitoring several clinical trials in Canada;

(e) Responsible for external biotechnology assessment and transfer.

5. TORONTO WESTERN HOSPITAL 1965-1987

(i) **Director, Division of Nephrology, 1972-1987**

(a) Developed an internationally recognized academic nephrology division with a full range of clinical, teaching and research programs;

(b) Recruited five additional geographic full-time staff each of whom developed international reputations in clinical and/or basic research. Three of them are recognized as having made major therapeutic advances in haemodialysis, peritoneal dialysis, and renal transplantation;

(c) Created an environment in which everyone involved in the program, including allied services (nursing, laboratories, social services, etc.) functioned as a team whose goals were to provide optimal patient care in an atmosphere which fostered research and education;

(d) Developed an internationally recognized training program in Nephrology;

(e) Carried out all the usual functions of an academic physician including undergraduate and postgraduate teaching as well as serving on multiple departmental, hospital and university committees.

(ii) **Director, Dialysis and Transplantation Program, 1965-1972**

(a) Started Ontario's first formal dialysis and renal transplantation program which by 1987 had developed into one of Canada's 1,000 renal transplants performed;

(b) In connection with the program, initiated the following external support functions:

- The Ontario Branch of the Kidney Foundation of Canada
- The first transplant organ sharing network in Ontario
- The organ donor publicity program including having a consent form placed on the driver's license.

6. POST GRADUATE AND SPECIALTY TRAINING 1957-1965

1962-1965 Subspecialty Training in Nephrology - Methodist Hospital, Houston, Texas

1960-1962 Internal Medicine and Pathology - Royal Victoria Hospital, Montreal, Quebec

1958-1959 General Practice - Sudbury and Cambridge, Ontario

1957-1958 Internal Medicine - Shaughnessy DVA Hospital, Vancouver, B.C.

7. EDUCATION AND SPECIALTY QUALIFICATIONS

1956 M.D. - University of Toronto

1963 Fellow - Royal College of Physicians and Surgeons of Canada

1964 Diplomate - American Board of Internal Medicine

8. PROFESSIONAL APPOINTMENTS

1983-1985 President, Kidney Foundation of Canada (Ontario Branch)

1982-1983	President, Canadian Transplantation Society
1980-1984	Co-ordinator, Undergraduate Clinical Methods Teaching, Toronto Western Hospital, Toronto
1980-1984	Chairman, Medical Education Committee, Department of Medicine, Toronto Western Hospital, Toronto
1974-1975	President, Medical Staff Association, Toronto Western Hospital, Toronto
1972	Associate Professor, Department of Medicine, University of Toronto
1970-1974	Co-ordinator, Postgraduate Nephrology Training Program, University of Toronto

9. MEMBERSHIPS

1981	Member, Canadian Transplantation Society (Founding)
1977	Member, Canadian Society for Immunology
1975	Member, American Society of Transplant Surgeons & Physicians
1972	Member, International Society of Nephrology
1970	Member, American Society of Artificial and Internal Organs
1969	Member, International Transplantation Society
1967	Member, Canadian Society of Nephrology (Founding)
1966	Member, American Society of Nephrology

10. AWARDS

1991	Initial recipient of Kidney Foundation (Ontario Branch) Annual Distinguished Service Award (created in my name)

1990	David Ornstein National Distinguished Service Award Kidney Foundation of Canada
1966	Best Clinical Teacher, Department of Medicine Toronto Western Hospital

EXHIBIT 2

BIBLIOGRAPHY-GEORGE A. DEVEBER

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2. Fluid and Electrolyte Problems in the Postoperative Period. Nursing Clinics of North America: 275-284 (1966)

3. Cyclophosphamide Therapy in Adult Glomerulonephritis. Laval Med. 39: (1968)

4. Effect of Haemodialysis on Thyroid Function. deVeber, G.A. and Schatz, D.L. Proc. European Dialysis & Transplant Ass. 226-229(1968)

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